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EDITORIAL

Natural killer reprogramming in cutaneous T-cell lymphomas: Facts and hypotheses

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Abstract

To better understand the pathogenesis of Sézary cells, distinguish them from reactive skin-infiltrating T-cells and improve disease treatment, efforts have been made to identify molecular targets deregulated by the malignant process. From immunophenotypic analysis and subtractive differential expression experiments to pan-genomic studies, many approaches have been used to identify markers of the disease. During the last decade several natural killer (NK) cell markers have been found aberrantly expressed at the surface of Sézary cells. In particular, KIR3DL2/CD158k, expressed by less than 2% of healthy individuals $CD4^+$ T-cells, is an excellent marker to identify and follow the tumor burden in the blood of Sézary syndrome patients. It may also represent a valuable target for specific immunotherapy. Other products of the NK cluster on chromosome 19q13 have been detected on Sézary cells, raising the hypothesis of an NK reprogramming process associated with the malignant transformation that may induce survival functions.

Key words: Sézary syndrome; Mycosis fungoides; Natural killer receptors; KIR3DL2; Cutaneous T-cell lymphomas

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INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of lymphoproliferative disorders involving primarily the skin. The most common subtypes of CTCL are mycosis fungoides (MF) and Sézary syndrome (SS). MF is characterized by a slowly progressing skin invasion by clonally derived mature $CD4^+$ T-lymphocytes, these malignant cells residing primarily in the infiltrating skin lesion. SS is a more aggressive leukemic and erythrodermic form of CTCL involving malignant $CD4^+CD45RO^+$ T-cells. Despite the fact that MF and SS are classified as distinct disease entities, their clinical relationship is still a matter of debate as they share common features and similarities suggesting that they might be variants of the same disease spectrum[1-3]. Patients with transformed MF can have blood findings characteristic of SS and can sometimes develop typical SS[4]. On the other hand, the majority of patients diagnosed with early-stage MF will never progress to advanced-stage disease. The finding that MF and SS arise from two distinct functional T-cell subsets, central memory for SS ($CCR7^+$L-selectin$^+$ $CD27^+CCR4^+CLA^{+/-}$) *vs* effector memory T cells for MF ($CCR7^-$L-selectin$^-$ $CD27^-$ $CCR4^+CLA^+$), if confirmed, favors the notion that they should be considered as separate lymphomas[5].

The prognosis of MF and SS depends on the type and extent of skin lesions and extracutaneous disease. This is reflected in the TNMB classification of MF/SS defined by the International Society for Cutaneous Lymphomas, involving evaluation of the skin (T), lymph nodes (N), visceral organs (M) and blood (B)[6]. SS is thus defined as meeting T4 plus B2 criteria, where T4 refers to a confluence of erythema covering at least 80% of the body surface area and B2 a high blood tumor burden[6]. Peripheral blood studies are important for establishing the diagnosis and staging for SS. While determining the tumor mass by histological examination of blood smears, with Sézary cells defined by a cerebriform nuclear morphology, is widely used and valuable, flow cytometry analysis of T-cell blood subsets provides a more objective and reproducible means to quantify and track blood involvement in patients with MF/SS. For example, a CD4:CD8 ratio higher than 10 is observed in about 80% of patients with SS, whereas loss of CD7 ($CD4^+CD7^- \geqslant 30\%$) or CD26 ($CD4^+CD26^- \geqslant 40\%$) are found in about half of the SS patients[7-9]. However, although it is possible to show using Vß-specific TCR antibodies that clonally expanded cells in SS may have these immunophenotypes, loss of CD7 or CD26 among $CD4^+$ T-cells can also be found in benign inflammatory erythroderma or even healthy blood. SS is considered as a clonal expansion of a T-cell subset and the analysis of T-cell clonality by PCR amplification of TCR-γ or -ß chain genes can allow the detection of a dominant T-cell clone in the peripheral blood in most SS patients. However, a T-cell clonality can also be detected in 34% of cases with benign inflammatory erythroderma[10]. Therefore the identification of a predominant T-cell clone might reflect a reactive rather than a neoplastic T-cell clone. The evaluation of other potential Sézary cell markers is consequently important for the diagnosis, prognosis and follow-up of SS. Among the proposed potential markers, several belong to the natural killer (NK) cell lineage, raising the question of a hypothetical NK-cell reprogramming mechanism occurring in the transformation of some CTCL. This editorial will focus on that provocative question.

THE NK RECEPTOR KIR3DL2/CD158K ON SS LYMPHOCYTES

Malignant T cells in MF and SS produce and respond to various cytokines in their microenvironment. Among them, interleukin (IL)-7 is sufficient to enhance the proliferation of healthy skin resident T-cells and is necessary to sustain an *in vitro* proliferation of malignant T-cells from SS or MF[11-13]. The observation that IL7-trangenic mice develop cutaneous lymphomas at high frequency further illustrates the role of this cytokine in inducing the proliferation of skin infiltrating lymphocytes[14]. This allowed us to develop T-cell lines derived from circulating Sézary cells as attested by their expression of TCR-Vß and TCRß-VDJ sequences identical to the *in vivo* tumor cells[15,16]. Such long-term cultured cell lines have been valuable tools to study Sézary cells and were used to initially describe their expression of KIR3DL2/CD158k[17].

The cell surface receptor KIR3DL2/CD158k belongs to the killer immunoglobulin-like receptor (KIR) family and is normally expressed by minor subsets of circulating NK cells and cytotoxic $CD8^+$ T-lymphocytes. The KIRs display a clonally distributed expression in human NK cells and KIR3DL2/CD158k is only expressed on a few percentage of circulating blood lymphocytes[18]. The KIR nomenclature is based on the biochemical structure of the receptors. Thus, they may have 2 (2D) or 3 (3D) extracellular immunoglobulin domains associated with a long (L) or short (S) cytoplasmic tail, responsible for an inhibiting or activating signaling activity respectively. KIRs recognize mainly determinants shared by a group of HLA class- I allotypes. The KIR3DL2/CD158k is an inhibitory receptor with specificity for HLA-A3 and -A11[18] and has been reported recently to also recognize CpG oligodeoxynucleotides[19].

Our group has identified KIR3DL2/CD158k as a new phenotypic marker for circulating Sézary cells[17,20,21]. Despite the lack of commercially available anti-CD158k antibodies other groups have confirmed these observations[8,22]. The proportion and absolute count of $CD158k^+$ lymphocytes strongly correlate with the percentage and absolute count of atypical cells determined by cytomorphology[20]. Interestingly, $CD158k^+$ cells can be detected even in SS patients with low tumor burden[20,22]. The $CD4^+CD158k^+$ cells found in the blood were shown to correspond to the malignant clonal cell population as assessed by the immunoscope technique [21]. In the skin, KIR3DL2/CD158k transcripts were found to be significantly overexpressed in SS compared to erythrodermic inflammatory diseases[23]. The only occasional expression of KIR3DL2/CD158k on rare $CD4^+$ T-cells from healthy individuals makes it a valuable positive marker to identify malignant Sézary cells, even when present at low levels, and to monitor the tumor cell load during therapy. In some cases however, CD158k expression may not identify all the neoplastic T-cells, due to clonal evolution during tumoral progression[24]. This raises the question of whether the appearance of CD158k is a relatively late event in the SS pathogenesis, occuring when genetic deregulation increases, or if it parallels the early oncogenic events. No definitive answer can be given but one may note that in normal T-cells KIR expression occurs after T-cell activation, and that in MF no $CD158k^+$ T-cells are detected in the skin at the patch-plaque stage but can be found in patients at the transformed stage, favoring the acquisition of KIR3DL2/CD158k expression as a late event[25]. It remains to understand what can be the consequences of this expression on the tumor cell biology in terms of proliferation or survival. CD158k/KIR3DL2 is an inhibitory receptor that upon engagement mediates an inhibitory signaling cascade through the ITIM domains located within its cytoplasmic tail. One can specu-

late that it may down regulate TCR-mediated signaling, in line with the reported hyporesponsiveness of Sézary cells to an anti-CD3 mAb stimulation[12]. This may be seen as an advantage for tumor cells to resist to antigen receptor-mediated cell death associated to chronic antigenic stimulation, as observed on normal T-cells. However, as what was recently observed, KIR may act differently on Sézary cells, and behave as co-activating receptors through a JNK-dependent pathway[26]. Clearly the exact function of KIR3DL2/CD158k in T-cells from SS patients has still to be defined. In a lower proportion of patients KIR3DL2 is not the only KIR expressed by Sézary cells. In particular, a significant expression of CD158a/KIR2DL1 and CD158b/KIR2DL2/3 can be observed in less than 10% of patients[22,26].

OTHER NK RECEPTORS ON SS CELLS

An abnormal expression of other NK receptors has been observed at the surface of Sézary cells. The CD85j/Ig-like transcript 2 (ILT2) receptor belongs to a family of receptors homologous to the KIR, encompassing both inhibitory forms recruiting SHP-1 phosphatase and short-tailed activating forms[27-29]. ILT2 is an inhibitory receptor specific for an a3-domain epitope shared by many MHC class Ia and Ib molecules and the class I -like protein UL18 of human cytomegalovirus[30]. It is expressed by myeloid cells, B lymphocytes and some NK and $CD8^+$ T-cells with memory phenotype[31]. Most circulating $CD4^+$ lymphocytes fail to express ILT2 at their cell surface, whereas the molecule is in fact present in the cytoplasm of all T-cells[32]. As for KIR, its action on circulating $CD8^+$ T-cells is to reduce antigen driven activation-induced cell death without affecting proliferation and survival induced by cytokines and particularly IL-7[31]. In SS, circulating malignant Sézary cells may be distinguished from non malignant reactive $CD4^+$ autologous T-cells through the detection of ILT2 at the cell surface[33]. In addition these receptors are functional as they can inhibit an anti-CD3 mAb-induced signaling and therefore perpetuate the survival of SS malignant cells by protecting them from CD3/TCR engagement induced apoptosis. Of note, in the skin, MF cells lack expression of ILT2[33].

Another essential NK cell marker reported at the surface of Sézary cells is NKp46/NCR1 that is not detected on normal circulating $CD4^+$ T-cells[34]. NKp46/NCR1, together with NKp44/NCR2 and NKp30/NCR3, forms the family of activating natural cytotoxicity receptors(NCR)[35]. These receptors are normally confined to NK cells, and their engagement induces strong activation of NK-mediated cytolysis. However, umbilical cord blood $CD8^+$ T-cells, when stimulated for a long period of time with IL-15, expressed NKp30 and NKp44, although only NKp30 was functional to induce cytotoxicity[36]. Whereas NKp30 and NKp46 expression are constitutive, NKp44 is acquired upon activation of NK cells. NKp46 mediates signal transduction through its association with the ITAM-bearing molecules CD3ξ or FceRIγ, that become tyrosine phosphorylated upon receptor cross-linking. NKp46 was detected at the surface of malignant Sézary cells in the absence of external stimulus. This expression, that parallels the one of KIR3DL2/CD158k, is specific to Sézary cells as it is not detected on cells isolated from MF or inflammatory erythroderma patients[34]. In NK cells, NKp46 acts as a full receptor and its engagement triggers their natural cytotoxicity against target cells. In Sézary cells however, its triggering does not induce CD3ξ tyrosine phosphorylation and fails to initiate the activating events leading to cell proliferation. In fact, when brought to close proximity to the CD3/TCR, NKp46 prevents the phosphorylation of CD3 chain, resulting in an overall inhibition of the TCR-mediated activation pathway. As mentioned above, SS cells are usually hyporesponsive to CD3/TCR-mediated triggering, which can be seen as a way to escape to antigen receptor-mediated cell death associated to chronic antigenic stimulation of T-cells. One can speculate that whereas KIR can mediate proliferation through JNK activation pathway, NKp46 may downregulate TCR signaling to promote survival. Could such a behavior reflect a perversion of normal functions when placed in an ectopic environment?

NK REPROGRAMMING IN T-CELL TRANSFORMATION

Cell transformation and tumoral progression is generally associated with a reprogramming of the cell differentiation program. Celiac disease (CD) is a chronic inflammation of the small intestine secondary to gluten intolerance. This leads to a chronic activation of the intraepithelial lymphocytes (IEL), that are tissue specialized $CD8^+$ cytotoxic T-lymphocytes, and to the alteration of the intestinal mucosa and the progression towards enteropathy-associated T-cell lymphoma[37]. IL-15 production, which is greatly increased in the mucosa of patients with CD, has an important role in the disease process[38]. Subjects expressing HLA-DQ2/DQ8, that form stable complexes with gluten peptides, elicit exacerbated response of DQ2/DQ8-restricted $CD4^+$ T-cells leading to villous atrophy and malabsorption. However, despite the expansion of IEL in the mucosa, gluten-specific IEL are rare or absent[39]. In fact, in CD patients, a massive expansion of few IEL cytotoxic T-cell clones that have undergone a genetic reprogramming under the IL-15 stimulation occurs, that essentially convert them into NK-like cells capable of cytolysis independently of a CD3/TCR signaling[40]. This reprogramming consists in the aberrant expression on these IEL of a panoply of normally restricted cytolytic NK lineage receptors, such as NKG2C, NKp44, NKp46, or KIR. Such reprogramming has also been reported in the cytotoxic T-cells from cytomegalovirus-seropositve patients[41]. This raises the question whether NK reprogramming may underlie the transformation of chronically stimulated T-cells.

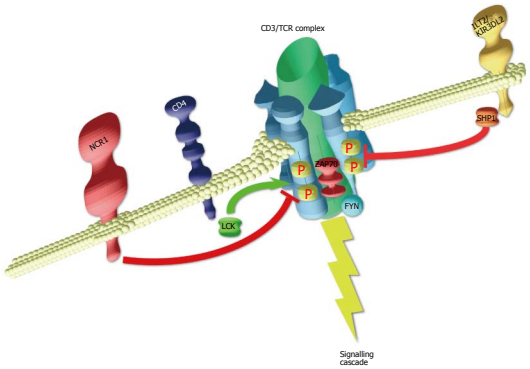

Figure 1 Tuning CD3/T cell receptor signalling threshold by natural killer receptors on Sézary tumoral cells. Ig-like transcript 2 (ILT2) or KIR3DL2 receptors on Sézary cells lower the threshold of T-cell receptor activation through the activation of the SHP1 phosphatase. Natural cytotoxicity receptors (NCR)1 (NKp46) receptors associate with CD3z-g chains and, when in close proximity, the NCR1 prevents the phosphorylation of CD3z chains of the T cell receptor complex. These mechanisms can be seen as a way to escape antigen-receptor mediated cell death associated with chronic T-cell stimulation in Sézary syndrome.

In SS, the aberrant expression of NK-cell lineage receptors such as KIR, ILT2 or NKp46 has been observed, that are all encoded in the NK cluster region on chromosome 19q13. Although the Sézary cells do not acquire cytotoxic capacity, signaling capacity through these receptors were observed in the malignant SS cells, suggesting an NK-like differentiation process. Chronic stimulation through antigen or allergen has been proposed to play a role in SS and MF[42]. With this perspective, Figure 1 illustrates how NK receptors may interfere with T-cell stimulation in Sézary cells, tuning the signalling threshold of the CD3/TCR, preventing the tumoral cells from activation-induced cell apoptosis. Of note a high level of T-cell stimulating cytokines is present in the skin, such as IL7. Elevated levels of IL-15, an important cytokine for NK reprogramming in CD, have been reported in SS[43,44]. Could there be a concerted aberrant expression of NK markers at the surface of Sézary cells, playing an important role in the pathobiology and tumoral progression of SS? Future work will tell us the truth, but that track is worth to be followed.

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